General

Guideline Title

Routine cerebrospinal fluid (CSF) analysis.

Bibliographic Source(s)

Deisenhammer F, Bartos A, Egg R, Gilhus NE, Giovannoni G, Rauer S, Sellebjerg F, Tumani H. Routine cerebrospinal fluid (CSF) analysis. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 5-17. [72 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Deisenhammer F, Bartos A, Egg R, Gilhus NE, Giovannoni G, Rauer S, Sellebjerg F, EFNS Task Force. Guidelines on routine cerebrospinal fluid analysis. Report from an EFNS task force. Eur J Neurol 2006 Sep;13(9):913-22.

Recommendations

Major Recommendations

The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point [GPP]) are defined at the end of the "Major Recommendations" field.

Cerebrospinal fluid (CSF) should be analysed immediately (i.e., <1 h) after collection. If storage is required for later investigation this can be done at 4º to 8º C (short term) or at –20º C (long term). Only protein components and ribonucleic acid (RNA) (after appropriate preparation) can be analysed from stored CSF (GPP).

The Level B recommendation regarding CSF partitioning and storage states that 12 mL of CSF should be partitioned into three to four sterile tubes. It is important that the CSF is not allowed to sediment before partitioning. Store 3–4 mL at 4º C for general investigations, cultivation and microscopic investigation of bacteria and fungi, antibody testing, polymerase chain reaction (PCR), and antigen detection. Larger volumes (10 to 15 mL) are necessary for certain pathogens like *Mycobacterium tuberculosis*, fungi or parasites.

Normal CSF protein concentration should be related to the patient's age (higher in the neonate period and after age of 60 years) and the site of lumbar puncture (LP) (Level B). Exact upper normal limits of protein concentration differ according to technique and examining laboratory.

The CSF to serum albumin concentration quotient (Q_{alb}) should be preferred to total protein concentrations, partly because reference levels are more clearly defined and partly because it is not confounded by changes in other CSF proteins (Level B).

The glucose concentration in CSF should be related to the blood concentration. Therefore, CSF glucose/serum ratio is preferable. Pathological changes in this ratio or in lactate concentration are supportive for bacterial or fungal meningitis or leptomeningeal metastases (Level B).

Intrathecal immunoglobulin G (IgG) synthesis can be measured by various quantitative methods, but at least for the diagnosis of multiple sclerosis (MS) the detection of oligoclonal bands by appropriate methods is superior to any existing formula (Level A). Patients with other diseases associated with intrathecal inflammation, for example patients with central nervous system (CNS) infections, may also have intrathecal IgA and IgM synthesis as assessed by non-linear formulae (Reiber hyperbolic formulae or extended indices), which should be preferred to the linear IgA and IgM indices (Level B).

Cellular morphology (cytological staining) should be evaluated whenever pleocytosis is found or leptomeningeal metastases or pathological bleeding is suspected (Level B). If cytology is inconclusive in case of query CSF bleeding, measurement of bilirubin is recommended for up to 2 weeks after the clinical event.

For standard microbiological examination sedimentation at 3000 x g for 10 min is recommended (Level B). Microscopy should be performed using Gram or methylene blue, Auramin O or Ziehl-Nielsen (*M. tuberculosis*), or Indian ink stain (*Cryptococcus*). Depending on the clinical presentation, incubation with bacterial and fungal culture media can be useful. Anaerobic culture media are recommended only if there is suspicion of brain abscess. A viral culture is generally not recommended. A list of infectious agents and their association with different diseases as well as the recommended method of detection is provided in Table 1.4 in the original guideline document. The results of bacterial antigen detection have to be interpreted with respect to the microscopical CSF investigation and culture results. It is not routinely recommended in cases of negative microscopy. A diagnosis of bacterial nervous system infection based on antigen detection alone is not recommended (risk of contamination).

CSF laboratories need to participate in regular internal and external quality assessment (Level A). In addition, to avoid possible erroneous differential diagnostic interpretations due to inadequate CSF findings, clinicians should make sure that the co-operating laboratory adheres to the essential quality standards (proof of education and training, certification of the CSF laboratory, continuous participation in internal and external controls) (GPP).

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Rating of Recommendations

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Good Practice Point When only class IV evidence was available but consensus could be reached, the task force has offered advice as Good Practice Points.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Neurological diseases requiring cerebrospinal fluid (CSF) analysis

Guideline Category

Diagnosis

Evaluation

Clinical Specialty

Internal Medicine

Neurology

Pathology

Intended Users

Clinical Laboratory Personnel

Physicians

Guideline Objective(s)

To produce recommendations on how to use a set of cerebrospinal fluid (CSF) parameters (including protein, albumin, immunoglobulin, glucose, lactate and cellular changes, as well as specific antigen and antibody testing for infectious agents) in different clinical settings and to show how different constellations of these variables correlate with diseases of the nervous system

Target Population

Patients with neurological diseases requiring investigation of cerebrospinal fluid (CSF)

Interventions and Practices Considered

1. Routine cerebrospinal fluid (CSF) analysis including total protein, albumin, immunoglobulins, glucose, lactate, cell count, cytological staining, and investigation of infectious CSF
2. Regular laboratory quality assessment

Major Outcomes Considered

Sensitivity and specificity of cerebrospinal fluid analysis

Methodology

Methods Used to Collect/Select the Evidence

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A Medline search using the search terms cerebrospinal fluid (CSF), immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin A (IgA), and albumin was conducted. Also, the key words 'cerebrospinal fluid' or 'CSF' were cross-referenced with 'glucose', 'lactate', 'cytology', 'cell* in title' excluding 'child*'. Furthermore, a search for 'cerebrospinal fluid' and 'immunoglobulin' and 'diagnosis' and 'electrophoresis' or 'isoelectric focusing' was performed limited to the time between 1 January 1980 and 1 January 2005, and returned only items with abstracts, and English language (274 references). A search for 'cerebrospinal fluid' AND 'infectious' limited for time (1 January 1980 until now) returned 560 abstracts. Abstracts which primarily did not deal with diagnostic issues and infectious CSF (e.g., non-infectious inflammatory diseases, vaccination, general CSF parameters, pathophysiology, cytokines and therapy) were excluded resulting in 60 abstracts. Searching the items 'cerebrospinal fluid' AND 'serology' limited for time (1 January 1980 until now) and excluding abstracts not directly related to the topic returned 35 abstracts and a search for 'cerebrospinal fluid' AND 'bacterial culture' limited for time (1 January 1980 until now) resulted in 28 abstracts.

For the current update (deadline October 2009) all the above search terms and selection criteria were applied for the time between 2005 and now.

Because this was not included in the first edition an additional Medline search for the items 'cerebrospinal fluid analysis' AND 'quality assurance' from 1981 until now returned 87 references. Only 15 of these references dealt primarily with quality assurance aspects of cerebrospinal fluid analysis.

The abstracts were selected by the author in charge of the respective topic. In addition, text books and articles identified in reference lists of individual papers were selected if considered appropriate.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Evidence was classified as Class I–IV according to the scheme agreed for European Federation of Neurological Societies (EFNS) guidelines (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Individual task force members prepared draft statements for various parts of the manuscript. Evidence was classified as Class I–IV and recommendations as Level A–C according to the scheme agreed for European Federation of Neurological Societies (EFNS) guidelines (see the "Rating Scheme for the Strength of the Recommendations" field). When only Class IV evidence was available but consensus could be reached, the task force has offered advice as Good Practice Points (GPP). The statements were revised and adapted into a single document which was then revised until consensus was reached.

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Good Practice Point When only class IV evidence was available but consensus could be reached, the task force has offered advice as Good Practice Points.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate analysis of cerebrospinal fluid (CSF)

Potential Harms

- Cytologic examination of cerebrospinal fluid (CSF) can render false-positive and false-negative results.
- Polymerase chain reaction (PCR) of CSF can render a false-negative result (most likely in the first 3 days after the illness or 10 days and more after the onset of the disease.)

Qualifying Statements

Qualifying Statements

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Sep (revised 2011)

Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

Source(s) of Funding

European Federation of Neurological Societies

Guideline Committee

European Federation of Neurological Societies Task Force on Routine Cerebrospinal Fluid (CSF) Analysis

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Financial Disclosures/Conflicts of Interest

The authors have reported no conflicts of interest.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies (EFNS) Web site .

Availability of Companion Documents

The following is available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on April 9, 2007. The information was verified by the guideline developer on May 15, 2007. This NGC summary was updated by ECRI Institute on February 20, 2012.

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